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Basic Pathology

sixth edition

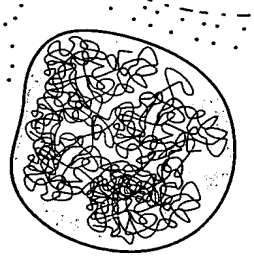

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Figure 16–27

Centrilobular hemorrhagic necrosis (nutmeg liver). The cut liver section, in which major blood vessels are visible, is notable for a variegated mottled red appearance, representing hemorrhage in the centrilobular regions of the parenchyma.

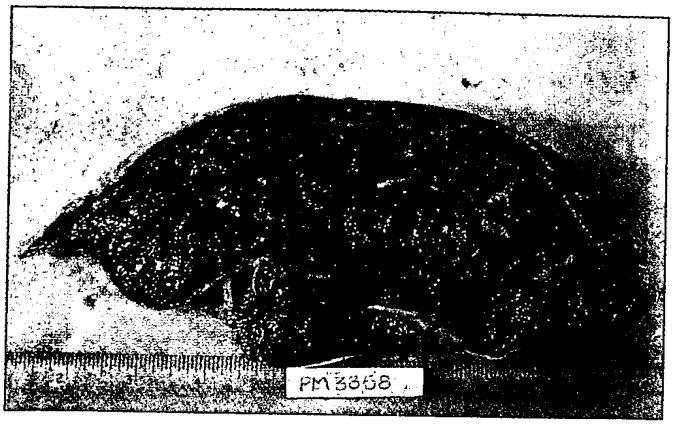

Figure 16–28

Budd-Chiari syndrome. Thrombosis of the major hepatic veins has caused extreme blood retention in the liver.

atis is a rare condition in which the dilation is primary. It is most commonly associated with exposure to anabolic steroids, and rarely oral contraceptives and danazol. The pathogenesis is not known. Although clinical signs are generally absent even in advanced peliosis, potentially fatal intra-abdominal hemorrhage or hepatic failure may occur. Peliotic lesions usually disappear after cessation of drug treatment.

Hepatic Venous Outflow Obstruction

Hepatic Vein Thrombosis (Budd-Chiari Syndrome). The Budd-Chiari syndrome was originally used to describe acute and usually fatal thrombotic occlusion of the hepatic veins. The definition has now been expanded to include subacute and chronic occlusive syndromes, characterized by hepatomegaly, weight gain, ascites, and abdominal pain. Hepatic vein thrombosis is associated with (in order of frequency) polycythemia vera, pregnancy, the postpartum state, the use of oral contraceptives, paroxysmal nocturnal hemoglobinuria, and intra-abdominal cancers, particularly hepatocellular carcinoma. All these conditions produce thrombotic tendencies or, in the case of liver cancers, sluggish blood flow. About 30% of cases are idiopathic.

With acutely developing thrombosis of the major hepatic veins or inferior vena cava, the liver is swollen, is red-purple, and has a tense capsule (Fig. 16–28). Microscopically, the affected hepatic parenchyma reveals severe centrilobular congestion and necrosis. Centrilobular fibrosis develops in instances in which the thrombosis is more slowly developing. The major veins may contain totally occlusive fresh thrombi, subtotal occlusion, or, in chronic cases, organized adherent thrombi.

The mortality of untreated acute Budd-Chiari syndrome is high. Prompt surgical creation of a portosystemic venous shunt permits reverse flow through the portal vein and improves the prognosis considerably; direct dilation of caval obstruction may be possible during angiography. The chronic form of the syndrome is far less grave, and about half the patients are alive after 5 years.

Veno-Occlusive Disease. Originally described in Jamaican drinkers of pyrrolizidine alkaloid–containing bush tea, veno-occlusive disease now occurs primarily in the immediate weeks after bone marrow transplantation. The incidence may approach 25% in recipients of allogeneic marrow transplants, with mortality rates of over 30%. Small hepatic vein radicles are obliterated by varying amounts of subendothelial swelling and fine reticulated collagen. The presumed cause is toxic endothelial injury, as from chemotherapy and radiation therapy given before marrow transplantation. In acute disease, there is striking centrilobular congestion with hepatocellular necrosis. As the disease progresses, connective tissue is laid down in the lumen of the venule.

TUMORS AND TUMOR-LIKE CONDITIONS

The liver and lungs share the dubious distinction of being the visceral organs most often involved in the metastatic spread of cancers. Indeed, *the most common hepatic neoplasms are metastatic carcinomas,* with colon, lung, and breast heading the list as sites of the primary tumor. The incidence of primary hepatic malignancies varies with the local prevalence of risk factors, particularly HBV infection.

Hepatic masses come to attention for a variety of reasons. They may generate epigastric fullness and discomfort or be detected by routine physical examination. Radiographic studies for other indications may pick up incidental liver masses. Important in the differential diagnosis of hepatic masses are (1) whether there is underlying liver disease, especially cir-

rhosis, in which the risk for primary hepatocellular carcinoma is high, and (2) whether the mass is solitary or multiple. Nonmalignant conditions are more likely to occur as single lesions in livers without preexistent disease, although some lesions (e.g., cysts) may be multiple.

Benign Tumors

The most common benign lesions are cavernous hemangiomas, identical to those occurring in other parts of the body (Chapter 10). These well-circumscribed lesions consist of endothelial cell-lined vascular channels and intervening stroma. They appear as discrete red-blue, soft nodules, usually less than 2 cm in diameter, often directly beneath the capsule. Their chief clinical significance is not to mistake them for metastatic tumors; blind percutaneous biopsy may incur severe intra-abdominal bleeding.

Solitary or multiple benign hepatocellular nodules may develop in the liver in the absence of cirrhosis. Focal nodular hyperplasia appears as a well-demarcated but poorly encapsulated nodule with a central fibrous scar, ranging up to many centimeters in diameter. It is believed to represent nodular regeneration in response to local vascular injury and is not a neoplasm per se. Focal nodular hyperplasia occurs most frequently in young to middle-aged adults and does not appear to pose a risk for malignancy.

LIVER CELL ADENOMA

This benign neoplasm of hepatocytes tends to occur in young women who have used oral contraceptives, and it regresses on discontinuance of their use. These tumors are pale, yellow-tan, well-demarcated, and frequently bile-stained nodules, found anywhere in the hepatic substance but often beneath the capsule. They may reach 30 cm in diameter. Histologically, liver cell adenomas are composed of sheets and cords of cells that may resemble normal hepatocytes or have some variation in cell and nuclear size. Portal tracts are absent; instead, prominent arterial vessels and draining veins are distributed through the substance of the tumor. Liver cell adenomas are significant for two reasons: (1) when they present as an intrahepatic mass, they may be mistaken for the more ominous hepatocellular carcinoma; and (2) subcapsular adenomas have a tendency to rupture, particularly during pregnancy (under estrogenic stimulation), causing life-threatening intra-abdominal hemorrhage. They harbor hepatocellular carcinoma only rarely.

Primary Carcinoma of the Liver

Primary carcinomas of the liver are relatively uncommon in North America and Western Europe (0.5% to 2% of all cancers) but represent 20% to 40% of cancers in many other countries. Most arise from hepatocytes, and are termed *hepatocellular carcinoma (HCC)*. Much less common are carcinomas of bile duct origin, cholangiocarcinomas, or tumors that are a mixture of the two cell types. Two rare forms are mentioned only: the hepatoblastoma, an aggressive hepatocellular tumor of childhood, and highly malignant angiosarcoma, which resembles those occurring elsewhere (Chapter 10). Primary liver angiosarcoma is of interest because of its association with exposure to vinyl chloride, arsenic, or Thorotrast, with latency periods of up to several decades.

Epidemiology. There are striking differences in the frequency of HCC in different nations of the world, linked strongly to the prevalence of HBV infection. Annual incidence rates of 3 to 7 cases per 100,000 population in North and South America, north and central Europe, and Australia compare with intermediate rates of up to 20 cases per 100,000 in countries bordering the Mediterranean. The highest frequencies are found in Taiwan, Mozambique, and Southeast China, where annual incidence rates among males approach 150 per 100,000. A common feature of high-incidence areas is onset of the HBV carrier state in infancy, after vertical transmission from infected mothers. This chronic carrier state may confer a 200-fold increased risk for HCC by adulthood. In these regions, cirrhosis may be absent in up to half of HCC patients. In the Western world, where HBV carriers are not common, cirrhosis is present in 85% to 90% of cases of HCC, frequently arising from other chronic liver diseases.

There is a pronounced male preponderance throughout the world, on the order of 3 : 1 in low-incidence areas and up to 8 : 1 in high-incidence areas, related to the greater prevalence of HBV infection, alcoholism, and chronic liver disease among males. Within each area, blacks have attack rates approximately fourfold higher than whites. In high-incidence areas, HCC generally arises early in adult life (third to fifth decades), whereas in low-incidence areas it is most often encountered in the sixth and seventh decades.

Pathogenesis. Several factors relevant to the pathogenesis of HCC were discussed in Chapter 6. Only a few points deserve emphasis at this time.

Three major etiologic associations have been established: infection with HBV, hepatocarcinogens in food (primarily aflatoxins), and chronic liver disease.

- Many factors, including age, sex, chemicals, viruses, hormones, alcohol, and nutrition, interact in the development of HCC. For example, the disease most likely to give rise to HCC is, in fact, the extremely rare hereditary tyrosinemia, in which almost 40% of patients develop this tumor despite adequate dietary control.
- The exact pathogenesis of HCC may vary between high-incidence, HBV-prevalent populations versus low-incidence Western populations, in which other diseases (such as alcoholism and genetic hemochromatosis) are more common.
- The development of cirrhosis appears to be an important, but not requisite, contributor to the emergence of HCC.

Extensive epidemiologic evidence links chronic HBV infection with liver cancer, and there is growing evidence implicating HCV infection. Molecular studies of HBV carcinogenesis reveal that the HBV genome does not contain any oncogenic sequences. Moreover, there is no selective site of integration of viral DNA into the host genome, precluding mutation or activation of a particular protooncogene. Rather, the following factors have been implicated:

- Repeated cycles of cell death and regeneration, as with chronic hepatitis, are important in the pathogenesis of HBV (and HCV) associated liver cell cancers.